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(54) **(R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]chromane as CNS active agent**

ZNS wirksames (R)-(-)-2-[5-(4-Fluorophenyl)-3-pyridylmethylaminomethyl]chroman

(R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane agissant sur le système nerveux central

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(56) References cited:
EP-A- 0 145 067
WO-A-93/17017
WO-A-95/05383
DE-A- 2 364 685
DE-A- 4 135 474
DE-A- 4 226 527

- **CHEMICAL AND PHARMACEUTICAL BULLETIN., vol.24, no.11, 1976, TOKYO JP pages 2661 - 2667 N. HIROSE ET AL. 'Studies on benzoheterocyclic derivatives. XVI. Synthesis and analgesic action of benzofuran derivatives.'**
- **CHIMICA THERAPEUTICA., vol.8, no.3, 1973, FR pages 259 - 270 C. GOLDENBERG ET AL. 'Benzofuran series. XLIX. Synthesis of aralkyl- and aryloxyalk yl(2,3-dihydro-2-benzofuryl)methylamines and related structures.'**
- **CHEMICAL ABSTRACTS, vol. 70, no. 7, 17 February 1969, Columbus, Ohio, US; abstract no. 28816q, H. SHOJI ET AL. '2-(Substituted aminomethyl)-2,3-dihydrobenzofurans.' page 308 ; & JP-A-68 018 131 (EISAI CO., LTD.)**
- **CHEMICAL ABSTRACTS, vol. 94, no. 13, 30 March 1981, Columbus, Ohio, US; abstract no. 103390x, H. TAKIZAWA ET AL. 'Substituted ethanolamines.' page 749 ; & DE-A-30 10 752 (KYOWA HAKKO KOGYO CO., LTD.)**
- **CHEMICAL AND PHARMACEUTICAL BULLETIN., vol.30, no.11, 1982, TOKYO JP pages 4092 - 4101 T. FUJIKURA ET AL. 'Studies on benzenesulfonamide derivatives with alpha- and beta-adrenergic antagonistic and antihypertensive activities.'**

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(Cont. next page)

EP 0 707 007 B1

- **CHEMICAL ABSTRACTS, vol. 86, no. 21, 23 May 1977, Columbus, Ohio, US; abstract no. 150434j, R.C. SAXENA ET AL. 'Effect of nicotine administration into the lateral cerebral ventricles of mice provides evidence for cholinergic mechanisms in the CNS.' page 27 ; & DRUGS AND CENTRAL SYNAPTIC TRANSMISSION, PAPERS OF A SYMPOSIUM, 1976, SASINGSTOKE, GB pages 139 - 144**
- **CHEMICAL ABSTRACTS, vol. 72, no. 21, 25 May 1970, Columbus, Ohio, US; abstract no. 109472t, J.H. OLIVER ET AL. 'Effect of reserpine and other drugs on the CNS and lethal effects of hyperbaric oxygen in mice.' page 224 ; & ARCHIVES INTERNATIONALES DE PHARMACODYNAMIE ET DE THERAPIE., vol.183, no.2, 1970, GHENT, BELG. pages 215 - 223**
- **PATENT ABSTRACTS OF JAPAN vol. 18, no. 19 (C-1152) 13 January 1994 & JP-A-05 255 302 (YAMANOUCHI PHARMACEUTICAL CO., LTD.) 5 October 1993**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

[0001] The invention relates to (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its physiologically acceptable salts thereof.

[0002] The object of the invention was to find novel compounds capable of being used for the preparation of drugs.

[0003] It has been found that (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible acid addition salts possess valuable pharmacological properties. Thus, in particular, it is active on the central nervous system, especially as serotonin agonist and antagonist. It inhibits the binding of tritiated serotonin ligands to hippocampal receptors (Cossery et al., European J. Pharmacol. 140 (1987), 143-155). It also modifies the accumulation of DOPA in the corpus striatum and the accumulation of 5-HTP in the nuclei raphes (Seyfried et al., European J. Pharmacol. 160 (1989), 31-41). It also has analgesic and hypotensive effects; thus, in catheterized, conscious, spontaneously hypertensive rats (strain: SHR/Okamoto/NIH-MO-CHB-Kisslegg; method: q.v. Weeks and Jones, Proc. Soc. Exptl. Biol. Med. 10 4 (1960), 646-648), the directly measured blood pressure is lowered after oral administration of the compounds. It is also useful for prophylaxis and control of the sequelae of cerebral infarction (Apoplexia cerebri) such as stroke and cerebral ischaemia.

The substance can be used in the treatment of diseases which are related to interferences in the serotoninergic and dopaminergic systems and which involve the receptors with high affinity to the 5-hydroxytryptamin (5HTIA type) or/and dopamin (D2 type) receptors.

[0004] It is suitable for the treatment of disorders of the central nervous system such as anxiety, tension and depression states, sexual dysfunctions caused by the central nervous system, disturbances in sleep or absorption of food. Furthermore, it is suitable to eliminate cognitive deficiencies, to improve powers of learning and memory and to treat Alzheimer's disease. They are also suitable for psychosis (schizophrenia).

(R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible acid addition salts can therefore be used as active ingredient for anxiolytics, antidepressants, neuroleptics, and/or antihypertensives, and also as intermediate for the preparation of other pharmaceutical active ingredients.

[0005] The invention relates to (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and to its biocompatible acid addition salts.

[0006] The invention further relates to a process for the preparation of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its salts, characterized in that 3-(chloromethyl)-5-(4-fluoromethyl)-pyridine is reacted with (R)-2-aminomethyl-chromane and/or in that the resulting base is converted into one of its salts by treatment with an acid.

[0007] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is otherwise prepared by methods known per se, such as those described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York), namely under reaction conditions such as those which are known and suitable for said reactions. It is also possible to make use of variants known per se, which are not mentioned in greater detail here.

If desired, the starting materials for the claimed process can also be formed in situ in such a way that they are not isolated from the reaction mixture but are immediately reacted further to give (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane.

[0008] The reaction of the educt compounds proceeds according to methods such as those known from the literature for the alkylation of amines. The components can be melted together in the absence of a solvent, in a sealed tube or an autoclave if necessary. It is also possible, however, to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene or xylene; ketones such as acetone or butanone; alcohols such as methanol, ethanol, isopropanol or n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidone; or nitriles such as acetonitrile, or else, if desired, mixtures of these solvents with one another or mixtures with water. It can be favourable to add an acid-binding agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or another alkali metal or alkaline earth metal salt of a weak acid, preferably a potassium, sodium or calcium salt, or to add an organic base such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the amine component. The reaction time is between a few minutes and 14 days, depending on the conditions used, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

[0009] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane possesses one centre of asymmetry. When prepared, it can therefore be obtained as racemate or else in the optically active form if optically active starting materials are used.

[0010] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane can be converted with an acid into the corresponding acid addition salt. Acids which produce biocompatible salts are suitable for this reaction. Thus it is possible to use inorganic acids, e. g. sulphuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid and sulphamic acid, as well as organic acids, i. e. specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulphonic or sulphuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethy-

lacetic acid. malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methanesulphonic or ethanesulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, p-toluenesulphonic acid, naphthalenemono-sulphonic and naphthalenedisulphonic acids and laurylsulphuric acid.

[0011] The invention further relates to the use of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible salts for the manufacture of pharmaceutical preparations, especially by a non-chemical route. For this purpose, it can be converted into a suitable dosage form together with at least one excipient or adjunct and, if appropriate; in combination with one or more additional active ingredients.

[0012] The invention further relates to compositions, especially pharmaceutical preparations, containing (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and/or one of its biocompatible salts. These preparations can be used as drugs in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral), parenteral or topical administration and which do not react with the novel compounds, examples of such excipients being water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, coated tablets, capsules, syrups, juices, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compound can also be lyophilized and the resulting lyophilizates used e.g. to manufacture injectable preparations.

[0013] The preparations indicated can be sterilized and/or can contain adjuncts such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, colourants, taste correctors and/or flavourings. If desired, they can also contain one or more additional active ingredients, e.g. one or more vitamins.

[0014] (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its biocompatible salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. It can be used for treating disorders of the central nervous system, such as tension, depressions and/or psychoses, and side-effects in the treatment of hypertension (e.g. with a-methyldopa). The compound can also be used in endocrinology and gynaecology, e.g. for the therapeutic treatment of acromegaly, hypogonadism, secondary amenorrhoea, premenstrual syndrome and undesired puerperal lactation, and also for the prophylaxis and therapy of cerebral disorders (e.g. migraine), especially in geriatrics in a manner similar to certain ergot alkaloids and for controlling the sequelae of cerebral infarction (Apoplexia cerebri), such as stroke and cerebral ischaemia.

Furthermore, it is suitable to eliminate cognitive deficiencies, to improve the power of learning and memory and to treat Alzheimer disease.

[0015] In these treatments, (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is normally administered analogously to known, commercially available preparations (e.g. bromocriptine. dihydroergocomin), preferably in dosages of between about 0.2 and 500 mg, especially of between 0.2 and 50 mg per dosage unit. The daily dosage is preferably between about 0.001 and 10 mg/kg of body weight. The low dosages (about 0.2 to 1 mg per dosage unit; about 0.001 to 0.005 mg/kg of body weight) are particularly suitable for use as anti-migraine preparations; dosages of between 10 and 50 mg per dosage unit are preferred for the other indications. However, the particular dose for each individual patient depends on a very wide variety of factors, for example the activity of the particular compound used, age, body weight, general state of health, sex, diet, time and method of administration, rate of excretion, drug combination and severity of the particular disease to which the therapy is applied. Oral administration is preferred.

[0016] In the following Examples, "working-up in conventional manner" means: Water is added if necessary, extraction is carried out with methylene chloride, the organic phase is separated off, dried over sodium sulphate and filtered, the filtrate is evaporated and the residue is purified by chromatography on silica gel and/or by crystallization. Temperatures are given in °C.

Preparation example

[0017] A solution of 2.8 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 2.2 g 3-(chloromethyl)-pyridine in 250 ml of DMF are stirred together with 1 g N-methylmorpholine for 12 hours at 20° and worked up in a conventional manner to give N-(3-pyridylmethyl)-N-(2-chromanyl-methyl)-amine. Stirring with 0.5 equivalents of maleic acid in 100 ml ethanol gives the maleate, m.p. 163-164°.

Preparation of the enantiomeric compound:

Example

[0018] A solution of 4,5 g 2-aminomethyl-chromane [obtainable by reacting 3-(2-hydroxy-phenyl)-propanal with KCN and subsequent catalytic reduction of the 2-cyano-chromane] and 3,9 g tosylproline in 190 ml ethanol are refluxed for 15 minutes. Afterwards the solution is cooled down to 5° while it is stirred. During the cooling

procedure a few crystalls of pure (R)-2-aminomethyl-chromane were added. The solution was kept under stirring at 5° for a period of 18 hours and afterwards the pure enantiomer (R)-2-aminomethyl-chromane was separated. The crystallisation process was repeated two times with the crystalls derived from the first crystallisation in order to yield an enantiomeric excess of more than 99 %.

[0019] Subsequently the (R)-2-aminomethyl-chromane was reacted with 3-(chloromethyl)-5-(4-fluorophenyl)-pyridine analogously to Preparation example to give (R)-(-)-2-[5-(4-fluorphenyl)-3-pyridyl-methylaminomethyl]-chromane [= (R)-(-)-1 N-[5-(4-fluorophenyl)-3-pyridylmethyl]-N-(2-chromanyl-methyl)-amine]. Stirring with 0,1 n hydrochloric acid solution yields the dihydrochloride, m.p. 234-235°; $[a^{20}]$ = -65° (c = 1, methanol). The examples below relate to pharmaceutical preparations.

Example A: Injection vials

[0020] A solution of 100 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and 5 g of disodium hydrogenphosphate in 31 of doubly distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterile filtered, filled into injection vials and lyophilized under sterile conditions, and the vials are closed in a sterile manner. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

[0021] A mixture of 20 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is fused with 100 g of soya lecithin and 1400 g of cocoa butter, and the mixture is poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

[0022] A solution of 1 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane, 9.38 g of $NaH_2PO_4.2H_2O$, 28.48 g of $Na_2HPO_4.12H_2O$ and 0.1 g of benzalkonium chloride is prepared in 940 ml of doubly distilled water. The solution is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

[0023] 500 mg of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane is mixed with 99.5 g of petroleum jell under aseptic conditions.

Example E: Tablets

[0024] A mixture of 100 g of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane, 1 kg of lactose, 600 g of microcrystalline cellulose, 600 g of maize starch, 100 g of polyvinyl-pyrrolidone, 80 g of talc and 10 g of magnesium stearate is pressed to give tablets in a customary manner, such that each tablet contains 10 mg of active compound.

Example F: Coated tablets

[0025] Tablets are pressed as stated in Example E and then coated in a customary manner with a coating of sucrose, maize starch, talc, tragecanth and colorant.

Example G: Capsules

[0026] Hard gelatin capsules are filled with (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane in the customary manner, so that each capsule contains 5 mg of active compound.

Example H: Inhalation spray

[0027] 14 g of(R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane is dissolved in 10 l of isotonic NaCl solution and the solution is filled into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or nose. One spray burst (about 0.1 ml) corresponds to a dose of about 0.14 mg.

Claims

1. (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and its physiologically acceptable salts thereof.

2. A process for the preparation of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane and its salts, **characterized in that** 3-(chloromethyl)-5-(4-fluoromethyl)-pyridine is reacted with (R)-2-aminomethyl-chromane,
and/or **in that** the resulting base is converted into one of its salts by treatment with an acid.

3. Process for the manufacture of pharmaceutical preparations, **characterised in that** (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridylmethylaminomethyl]-chromane and/or one of its biocompatible salts are converted into a suitable dosage form together with at least one solid, liquid or semiliquid excipient or adjunct.

4. Pharmaceutical preparation, **characterised in that** it contains (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane and/or one of its biocompatible salts.

5. Use of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane or its biocompatible salts for the manufacture of a drug.

6. Use of (R)-(-)-2-[5-(4-fluorophenyl)-3-pyridyl-methylaminomethyl]-chromane or its biocompatible salts, for the manufacture of a pharmaceutical for the treatment of disorders of the central nervous system

7. Use according to claim 6 in which the disorders of the central nervous system are anxiety, depression states, Alzheimer's disease or schizophrenia.

Patentansprüche

1. (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethyl-aminomethyl]chroman und physiologisch unbedenkliche Salze davon.

2. Verfahren zur Herstellung von (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman und Salzen davon, **dadurch gekennzeichnet, daß** man 3-(Chlormethyl)-5-(4-fluormethyl)pyridin mit (R)-2-Aminomethylchroman umsetzt, und/oder die so erhaltene Base durch Behandlung mit einer Säure in eines ihrer Salze umwandelt.

3. Verfahren zur Herstellung von pharmazeutischen Zubereitungen, **dadurch gekennzeichnet, daß** man (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethyl-aminomethyl]chroman und/oder eines seiner biokompatiblen Salze zusammen mit wenigstens einem festen, flüssigen oder halbflüssigen Hilfsmittel bzw. Zusatzstoff in eine geeignete Dosierungsform bringt.

4. Pharmazeutische Zubereitung, **dadurch gekennzeichnet, daß** sie (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman und/oder eines seiner biokompatiblen Salze enthält.

5. Verwendung von (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman oder biokompatiblen Salzen davon zur Herstellung eines Arzneimittels.

6. Verwendung von (R)-(-)-2-[5-(4-Fluorphenyl)-3-pyridylmethylaminomethyl]chroman oder biokompatiblen Salzen davon zur Herstellung eines Medikaments zur Behandlung von Erkrankungen des zentralen Nervensystems.

7. Verwendung gemäß Anspruch 6, wobei es sich bei den Erkrankungen des zentralen Nervensystems um Angstzustände, Depression, Alzheimer-Krankheit oder Schizophrenie handelt.

Revendications

1. (R)-(-)-2-[5-(4-Fluorophényl)-3-pyridylméthylaminométhyl]-chromane et ses sels acceptables d'un point de vue physiologique.

2. Procédé de préparation du (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane et de ses sels, **caractérisé en ce que** l'on fait réagir la 3-(chlorométhyl)-5-(4-fluorométhyl)pyridine avec le (R)-2-aminométhylchromane, et/ou **en ce que** l'on transforme la base résultante en un de ses sels par traitement avec un acide.

3. Procédé de fabrication de préparations pharmaceutiques, **caractérisé en ce que** le (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl] chromane et/ou un de ses sels biocompatibles sont mis sous une forme d'administration appropriée en même temps qu'au moins un excipient ou additif solide, liquide ou semi-liquide.

4. Préparation pharmaceutique, **caractérisée en ce qu'**elle contient du (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]-chromane et/ou un de ses sels biocompatibles.

5. Utilisation de (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane ou de ses sels biocompatibles pour la fabrication d'un médicament.

6. Utilisation de (R)-(-)-2-[5-(4-fluorophényl)-3-pyridylméthylaminométhyl]chromane ou de ses sels biocompatibles pour la fabrication d'un produit pharmaceutique destiné au traitement de troubles du système nerveux central.

7. Utilisation selon la revendication 6 dans laquelle les troubles du système nerveux central sont l'anxiété, les états dépressifs, la maladie d'Alzheimer ou la schizophrénie.